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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,569	08/22/2003	Brett P. Monia	ISPH-0759	9744

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Licata & Tyrrell P.C.
66 E. Main Street
Marlton, NJ 08053

EXAMINER	
ASHEN, JON BENJAMIN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/646,569	MONIA ET AL.	
	Examiner	Art Unit	
	Jon B. Ashen	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/22/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Claims 1-44 were canceled by Applicant in the communication filed February 20th, 2004. Claims 45-51 are currently pending and under examination in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 45-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting the growth, invasion or migration of melanoma tumors using an antisense compound 20 to 30 nucleobases in length targeted to human focal adhesion kinase (FAK) wherein said antisense compound comprises SEQ ID NO: 18, does not reasonably provide enablement for inhibiting tumor cell growth, invasion or migration of other tumors in any animal (including humans) using an antisense compound 20 to 30 nucleobases in length targeted to human FAK wherein said antisense compound comprises SEQ ID NO: 18 that is delivered systemically. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

Claims 45-51 are drawn broadly to a method of treating generally any tumor comprising the systemic delivery of an antisense compound 20 to 30 nucleobases in length targeted to human FAK wherein the method can further comprise administration of a chemotherapeutic agent that can be 5-fluorouracil. The nature of the instant invention is as a method of *in vivo* therapy using an antisense compound that is an antisense oligonucleotide that is 20 to 30 nucleobases in length that comprises a specified sequence (SEQ ID NO: 18).

The specification provides examples wherein cells *in vitro* (cell culture) are treated with antisense targeted to human FAK and the expression of FAK is inhibited. SEQ ID NO:18 is used to inhibit the migration of cells in an *in vitro* migration assay. The specification provides an example wherein SEQ ID NO:18 inhibits the expression of FAK in melanoma cells *in vitro* (cell culture) and this inhibition is enhanced by coadministration of 5-FU, *in vitro*. Finally, the specification provides an example wherein SEQ ID NO:18 is administered to a xenograft mouse model comprising a human melanoma and the growth and metastasis of human melanoma cells is inhibited. The specification does not

demonstrate that SEQ ID NO:18 is capable of inhibiting the growth *in vivo* of any non-melanoma tumor or of melanoma tumors *in vivo* (whole organism) when administered to an animal systemically. The prior art, as shown by Cance et al. (U.S. Patent 6,015,893), teaches that the growth, viability and invasiveness of melanoma cells can be inhibited when treated with antisense *ex vivo*, prior to administering the composition comprising the cells and antisense to an animal.

The state of the art at the time the instant invention was made, relative to the enablement of the antisense therapies *in vivo,* recognizes that there is a high degree of unpredictability in the art of applying antisense without direct evidence of therapeutic effect due to obstacles that continue, to the present day, to hinder the application of nucleic acid therapies *in vivo* (whole organism). Such obstacles include, for example, problems with delivery and target accessibility (see Opalinska et al., Check, Jen et al. below). Cell culture examples are generally not predictive of *in vivo* inhibition due to differences in metabolites and clearance rates, local concentration of antisense, and the potential for non-antisense side effects. The field of antisense generally, to date, does not provide guidelines by which antisense can be routinely targeted to generally any cell type *in vivo* (whole organism) at a concentration effective to result in a treatment effect. The following references discuss the problems of nucleic acid based therapies in reference to the claimed therapeutic antisense method.

Opalinska et al. 2002 (Nature Reviews, Vol. 1, pp. 503-514) provide a review of the challenges that remain before nucleic acid therapy becomes routine in therapeutic settings and clearly indicate that the art of nucleic acid therapy

remains highly unpredictable and unreliable, particularly *in vivo*. According to Opalinska et al., "Although conceptually elegant, the prospect of using nucleic acid molecules for treating human malignancies and other diseases remains tantalizing, but uncertain. The main cause of this uncertainty is the apparent randomness with which these materials modulate the expression of their intended targets. It is a widely held view that molecule delivery, and selection of which messenger RNA sequence to physically target, are core stumbling blocks that hold up progress in the field" (pg 503). Opalinska et al. also note that .. "[I]t is widely appreciated that the ability of nucleic acid molecules to modify gene expression *in vivo* is quite variable and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells, and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" (pg. 511).

In regards to the delivery of therapeutic nucleic acids, Jen et al. (Stem Cells 2000, Vol. 18, p 307-319) state (pg. 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery.... presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (pg. 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Check also states, in regards to delivery, that ""Scientists tried a variety of ways to get the antisense RNAs into cells ..... [B]ut antisense has not performed well in clinical trials, partly because these delivery systems were not particulary effective. Khvorova believes that the medical benefits of RNAi will be huge if the delivery issues can be resolved. "But we've looked at a lot of the delivery methods that have been used for antisense and so far I haven't been impressed," she says" (pg 11, col. 3, lines 4-15).

The specification has provided limited guidance for one skilled in the art to practice the invention claimed. However, this guidance would not have been sufficient to enable the skilled artisan to have practiced the claimed treatment methods over the broad scope claimed. One of the major hurdles to the *in vivo* (whole organism) application of antisense is the delivery of an antisense molecule to a target cell at a concentration effective to provide a therapy. The examples in the specification which demonstrate treatment effects for neovascularization provide guidance by which a treatment effect is provided when antisense can be delivered locally, by direct injection into the eye, at a high concentration and do not address the instantly claimed methods. The prior art method of Cance et al., of inhibiting melanoma cell viability, growth and invasiveness, are performed *ex vivo*, and do not provide guidance on systemic delivery. The claimed treatment methods, however, are drawn to delivery of antisense systemically, to generally any tumor cell, including melanoma cells, and inhibiting the growth of the tumor or the invasion or migration of the melanoma cells. The specification does provide a single example of treating a

melanoma tumor in a mouse, but the details of delivery are unspecified, as to whether direct, local administration was used, or if the antisense was delivered systemically.

The specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver antisense targeted to FAK *in vivo* (whole organism) wherein systemic delivery is required, particularly to deliver the antisense of the claimed invention at a concentration effective to result in the inhibition of tumor growth, or the reduction of melanoma cell invasion or migration. One skilled in the art would not be expected to be able to apply the limited guidance provided by the specification for local administration to general administration, nor would one skilled in the art be expected to be able to treat generally any tumor using SEQ ID NO: 18 based on the example of treating only melanoma tumors using SEQ ID NO:18. Given the unpredictability of antisense methods of treatment *in vivo* (whole organism), it is unclear that the *in vitro* examples using FAK antisense to inhibit the expression of FAK in adenocarcinoma cells would correlate with the inhibition of the growth, invasiveness or mitration of generally any tumor, including melanoma, *in vivo* (whole organism) using the antisense molecule of SEQ ID NO: 18.

In order to practice the invention, over the full scope claimed, one skilled in the art would have needed to perform undue de novo trial and error experimentation, beyond the teachings of the instant specification, in order to determine how to specifically deliver antisense targeted to FAK *in vivo* (whole organism) systemically to a target tumor cell at a concentration effective to

achieve a therapy for a tumor which cannot be treated by local/direct administration of an antisense molecule. Further, undue de novo trial and error experimentation would be required to determine whether or not any other tumor (besides melanoma) can be treated *in vivo* (whole organism) using SEQ ID NO:18 to inhibit tumor growth, invasion or migration. Additionally, this undue de novo trial and error experimentation would include the determination of such factors as dosage, route of aéministration, disposition of the antisense molecule in tissues, and the half-life and stability of the antisense molecule *in vivo* (whole organism) for the systemic delivery of SEQ ID NO: 18.

Given the art recognized unpredictability of the application of antisense *in vivo* (whole organism) this determination would not be routine, nor would the limited guidance provided for FAK antisense delivered locally be sufficient for one skilled in the art to deliver antisense systemically, to generally any target cell. Although antisense is considered to be a potential therapeutic, there are art-recognized limitations to its applicability *in vivo* (whole organism), particularly in regards to delivery, *in vivo* (whole organism) stability, *in vivo* accessibility and toxicity. To overcome the limitations to the *in vivo* (whole organism) application of antisense, one skilled in the art would require specific guidance to predictably apply antisense in the treatment of any tumor cell growth, invasion or migration. The specification does not provide this specific guidance for treatment of any tumor using a systemically delivered antisense molecule comprising SEQ ID NO: 18 nor does the antisense field to date have such general guidelines.

3. Claim 51 objected to because of the following informalities: Based on the disclosure of the specification as filed, the Examiner believes that "5-fluorourscil" set forth in line 2 of claim 51 was intended to read, "5-fluorouracil." Appropriate correction is required.

Conclusion

4. No claim currently under examination in this application is in condition for allowance.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jba

SEAN McGARRY
PRIMARY EXAMINER
1635